REMARKS/ARGUMENTS

Reconsideration and withdrawal of the rejections of the present application are respectfully requested in view of the amendments to the claims and remarks presented herewith, which place the application into condition for allowance.

Status of the Claims and Formal Matters

Claims 40-44 and 71 are currently pending in this application. Claims 45-70 and 72-77 have been withdrawn from consideration as allegedly being drawn to a non-elected invention an In order to advance prosecution and to overcome rejections, claim 43 had been cancelled and claims 40-42 and 44 had been amended without prejudice, admission, surrender of subject matter or intention of creating estoppel as to equivalents. Applicants hereby assert the right to reclaim withdrawn or cancelled subject matter in co-pending applications.

The amended claims 40-42 and 44 find support throughout the specification and specifically at paragraphs [0030], [0031], [0032], [0033], [0034], [0035] and [0036] of the published application US 20060194715. Moreover, as these changes do not narrow the scope of the originally claimed subject matter, the application of the doctrine of equivalents is not affected.

It is respectfully submitted that the amendments presented herein are made to clarify and round out the scope of protection to which Applicants are entitled, and not for purposes of patentability within the meaning of §§101, 102, 103, or 112.

Claim objections.

Claim 43 had been objected because of the alleged informalities. In view of cancellation of claim 43, the objections are now moot and should be withdrawn.

Rejections under §112, 1st paragraph

35 U.S.C. §112, First Paragraph - Written Description.

Claims 40-44 and 71 were rejected under 35 U.S.C. §112, 1st paragraph as allegedly failing to comply with the written description requirement. The Office Action contends that

claims 40-44 and 71 allegedly refer to protein only by function. Applicants respectfully traverse the rejection.

By this paper, claims 40-42 and 44 are amended to clarify that the ble fusion proteins may be used as an affinity tag to detect the protein of interest and to determine the folding state of the detected protein. Consequently, Applicants urge that this rejection is moot and should be withdrawn.

An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." *In re Gosteli*, 872 F.2d 1008, 1012, 10 USPQ2d 1111, 1117 (Fed. Cir. 1991). Stated otherwise, the test for sufficiency of support in an application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later-filed subject matter. *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985). Such a test is conducted from the standpoint of one of skill in the art at the time the application was filed. *Wang Labs v. Toshiba Corp.*, 993 F.2d 858, 865, 26 USPQ2d 1767, 1774 (Fed. Cir. 1993). Consequently, based on the knowledge of those skilled in the art at the time of filing, together with the disclosure provided in the instant specification, Applicants respectfully submit that amended claims 40-42, 44 and 71 satisfy the written description requirement under §112, 1st paragraph. Reconsideration and withdrawal of the §112, 1st paragraph rejection for an alleged failure to comply with the written description requirement is respectfully requested.

35 U.S.C. §112, First Paragraph – Enablement

Claim 71 has been rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the enablement requirement (Office Action, pages 4-5). The Office Action contends that the specification, while being enabling for an amine reactive surface, does not allegedly provide enablement for any surface from any source and/or origin via bleomycin antibodies. *Id.* Applicants respectfully traverse this rejection.

The test for enablement is whether one reasonably skilled in the art could make or use the claimed invention without undue experimentation, based on the disclosure in the application and the information available in the art. *United States v. Telectronics, Inc.*, 857 F.2d 778, 785 (Fed.

Cir. 1988); MPEP § 2164.01. The Office must consider many factors for enablement, including the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art, and the breadth of the claims. *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988); MPEP § 2164.01(a).

Applicants respectfully point to the significant guidance and working examples provided in the instant case. The instant application provides that amine reactive surface is one exemplary surface for coupling the bleomycin antibiotic to the surface (see [0036-0038], Example 1.3-1 6). The specification further states that "other functional groups present on the antibiotics may be used to couple the antibiotics to a surface, and this will be apparent to the person skilled in the art" (see [0038] of the published US 20060194715).

Applicants point out that various functional groups capable of coupling the antibiotics to the surface were well known prior to the filing of the instant application. As such, one of skill in the art could easily substitute other functional groups for the amine reactive surface during the coupling reaction (see for example, Exhibit 1, Journal of Antibiotics, Vol. 26 (1973), No. 4, pp. 252-254) or conjugate the antibiotic directly to a polymer which could be subsequently immobilized to a solid surface (see for example, Exhibit 2, US Patent 5,037,883). Thus, at the time of filing, the art included well known methods for using various functional groups in order to couple bleomycin antibiotic to the surface. *See, e.g., Wands*, 858 F.2d at 740; MPEP §2164.01(a).

Notably, the test for "undue experimentation" is not merely quantitative, and the time and difficulty of experimentation are not determinative. *Wands*, 858 F.2d at 737; MPEP §2164.06. A considerable amount of experimentation is permissible if it is merely routine or if the specification provides a reasonable amount of guidance for how the experimentation should proceed. *Wands*, 858 F.2d at 737; MPEP §2164.06. Where an invention involves biological activity, this itself does not constitute "undue experimentation," particularly where the level of skill is high (as noted in the instant case; *see* Office Action, page 7). *Wands*, 858 F.2d at 740. Furthermore, Applicants need only provide *sufficient* disclosure to teach those of skill in the art how to make and use the claimed invention. MPEP § 2164. The standard does not require

thousands of examples or every possible species for the claimed invention. *In re Angstadt*, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976).

Thus, the instant application provides considerable guidance and working examples for specific types of surfaces from different sources and/or origins which can be coupled with bleomycin antibiotics. Furthermore, the state of the art is replete with examples of other functional groups that may be used to couple the antibiotics to the surface. Therefore, taken together, at the time of filing, one of skill in the art would be able to practice the instant methods without undue experimentation. Thus, Applicants urge that the specification provides sufficient enablement for the claimed methods and respectfully request withdrawal of this rejection.

Rejections under § 112, second paragraph.

Claims 40-44 were rejected under 35 U.S.C. §112, 2nd paragraph as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention. In view of the amendments to claims 40-42 and 44 and cancellation of claim 43, Applicants urge that this rejection is moot and should be withdrawn. Again, as the changes did not affect the scope of the claimed subject matter, the application of the doctrine of equivalents is not affected.

Rejections under §102(a)

Claims 40-41 and 44 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Gautier et al., 1996, Experimental Cell Research 224, 291-301, "Gautier". The Office Action contends that Gautier allegedly discloses fusion genes carrying Drosophila alcohol dehydrogenase (Dro-ADH) fused to Sh ble, expressed in mammalian cells and thus anticipates the instant claims. This rejection is respectfully traversed in view of the claim amendments and remarks presented herewith.

The instant invention relates, *inter alia,* to the novel use of the family of ble genes, for example, Sh ble, Tn5 ble and Sa ble, and the family of proteins expressed by these genes which are able to reversibly bind to the bleomycin family of antibiotics. When these ble genes are expressed together with another protein as fusion proteins or the ble gene products are otherwise fused or linked to other molecules, particularly proteins, they can, for example, be used to strongly or weakly bind the fusion protein to a surface, such as an array, particular a microarray, a

glass slide or a microtitre plate (where strong binding is generally desired) as well as to, for example, beads or other similar forms which are used in affinity purification. The invention further relates to the use of ble fusion proteins as a folding and solubility marker.

Gautier relates to small fusion genes carrying phleomycin resistance and Drosophila alcohol dehydrogenase reporter properties and their subsequent application in retroviral vectors. Specifically, Gautier teaches sh ble fusions and uses them to confer resistance and reporter activity in the same polypeptide. The retroviral vectors in Gautier were inoculated in the E3 chick embryo and cells from different organs were later stained for ADH activity. However, Gautire does not does not teach, disclose, or suggest the capture and/or binding of she ble fusion proteins on a solid substrate via the she ble antibiotic binding pocket. Gautire does not relate to the She ble unusual property of stoichiometric antibiotic resistance wherein the mechanism of action is antibiotic binding rather than catalytic breakdown of the antibiotic. Due to these deficiencies, Gautire fails to enable instant method of detecting a protein of interest comprising ble fusion protein wherein said ble fusion protein is an expression and folding marker and/or an affinity tag.

Under §102, a reference can only be anticipatory if it enables that which it is alleged to anticipate. *Elan Pharmaceuticals v. Mayo Foundation for Medical Education and Research* 346 F.3d 1051, 68 U.S.P.Q.2d 1373, (Fed. Cir. 2003). Gautire also fails to teach or disclose all of the claim limitations, namely the recitation of a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Consequently, Applicants assert that a §102(b) rejection in view of Gautire is moot. Reconsideration and withdrawal of the rejection is hereby respectfully requested.

Claims 40-41 and 44 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Bennett et al., (1998 Bio Techniques 24(30): 478-482), "Bennett". The Office Action contends that Bennett allegedly teaches a ble fusion protein comprising green fluorescent protein (GFP) and Zeocin™-resistance gene Sh ble that can be allegedly used for visual

screening and selection of transfected mammalian cells. This rejection is respectfully traversed in view of the claim amendments and remarks presented herewith.

Bennett relates to fusions to generate a bifunctional protein for the identification and selection of transfected mammalian cells. This bifunctional protein was aimed to determine transient transfection efficiencies in tissue culture cells using fluorescence microscopy carrying phleomycin resistance and Drosophila alcohol dehydrogenase reporter properties and their subsequent application in retroviral vectors. However, Bennett does not teach, disclose, or suggest the capture and/or binding of she ble fusion protein on a solid substrate via the she ble antibiotic binding pocket. Furthermore, Bennett does not relate to the She *ble* unusual property of stoichiometric antibiotic resistance wherein the mechanism of action is antibiotic binding rather than catalytic breakdown of the antibiotic. Due to these deficiencies, Bennett fails to enable instant method of detecting a protein of interest comprising ble fusion protein wherein said ble fusion protein is an expression and folding marker and/or an affinity tag.

Under §102, a reference can only be anticipatory if it enables that which it is alleged to anticipate. *Elan Pharmaceuticals v. Mayo Foundation for Medical Education and Research* 346 F.3d 1051, 68 U.S.P.Q.2d 1373, (Fed. Cir. 2003). Bennett also fails to teach or disclose all of the claim limitations, namely the recitation of a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir.1987). Consequently, Applicants assert that a §102(b) rejection in view of Bennett is moot. Reconsideration and withdrawal of the rejection is hereby respectfully requested.

Claims 40-41 and 44 were rejected under 35 U.S.C. §102(b) as allegedly being anticipated by Baron et al., Gene, 1992, 15; 114(2):239-243, "Baron". The Office Action contends that Baron allegedly discloses She ble gene fused with E.coli lac Z in order to generate bifunctional β-galactosidase:phleomycin-resistance fusion protein as a potential marker for eukaryotic cells. This rejection is respectfully traversed in view of the claim amendments and remarks presented herewith.

Baron demonstrates the bifunctionality of She ble fusion 130 Kda hybrid protein in E.coli and in the fungus and Tolypocladium geodes. The Baron system appears to be a potentially useful tool for the direct selection of transformants in a wide variety of prokaryotic and eukaryotic hosts. However, Barron does not does not teach, disclose, or suggest the capture and/or binding of She ble fusion protein on a solid substrate via the She ble antibiotic binding pocket. Barron does not relate to the She ble unusual property of stoichiometric antibiotic resistance wherein the mechanism of action is antibiotic binding rather than catalytic breakdown of the antibiotic. Due to these deficiencies, Barron fails to enable instant method of detecting a protein of interest comprising *ble* fusion protein wherein said ble fusion protein is an expression and folding marker and/or an affinity tag.

Under §102, a reference can only be anticipatory if it enables that which it is alleged to anticipate. *Elan Pharmaceuticals v. Mayo Foundation for Medical Education and Research* 346 F.3d 1051, 68 U.S.P.Q.2d 1373, (Fed. Cir. 2003). Barron also fails to teach or disclose all of the claim limitations, namely the recitation of a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Consequently, Applicants assert that a §102(b) rejection in view of Barron is moot. Reconsideration and withdrawal of the rejection is hereby respectfully requested.

Rejections under §103(a)

Claims 42 and 43 were rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Blackburn et al. (WO 0227327), "Blackburn"in view of Bennett. The Office Action contends that it would have been obvious to the skilled artisan to create "tagged" ble fusion proteins by substituting a hexa-histidine tag disclosed by Blackburn for the GFP reporter protein disclosed by Bennett and purify the protein by Zeocin selection. The Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to

combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art references must teach or suggest all the claim limitations. MPEP §2143. A *prima facie* case of obviousness has not been established by the instant rejection of Blackburn in view of Bennett, because the references, considered either alone or in combination, fail to teach or suggest all the claim limitations. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974).

Blackburn relates to methods of producing proteins in which one or more domains are full length and correctly folded and which are each tagged at either the N or C-terminus with one or more marker moieties and arrays containing such proteins. Blackburn does not provide requisite suggestion or motivation that would lead the skilled artisan to arrive at the instant method of detecting a protein of interest comprising ble fusion protein wherein said ble fusion protein is an expression and folding marker and/or an affinity tag.

Bennett does not remedy the deficiencies of Blackburn. As discussed above, Bennett relates to fusions to generate a bifunctional protein for the identification and selection of transfected mammalian cells. This bifunctional protein was aimed to determine transient transfection efficiencies in tissue culture cells using fluorescence microscopy carrying phleomycin resistance and Drosophila alcohol dehydrogenase reporter properties and their subsequent application in retroviral vectors. However, nothing in Bennett would cause the ordinary scientist to extrapolate the capture and/or binding of She ble fusion protein on a solid substrate via the She ble antibiotic binding pocket. Furthermore, Bennett is silent with regard to the She ble unusual property of stoichiometric antibiotic resistance wherein the mechanism of action is antibiotic binding rather than catalytic breakdown of the antibiotic.

Thus, Blackburn and Bennett fail, both alone and in combination to teach, suggest or motivate a skilled artisan to practice the instantly claimed invention. The Office Action contention is unsupported and, at best, amounts to an 'obvious to try" standard to arrive at the instant method of detecting a protein of interest comprising ble fusion protein wherein said ble fusion protein is an expression and folding marker and/or an affinity tag. However, "obvious to try" is not the relevant standard for obviousness and the Section 103 rejection must fail for this reason as well.

CONCLUSION

Favorable action on the merits is respectfully requested. If any discussion regarding this Response is desired, the Examiner is respectfully urged to contact the undersigned at the number given below, and is assured of full cooperation in progressing the application to allowance.

Applicants believe no additional fees are due with the filing of this Response. However, if any additional fees are required or if any funds are due, the USPTO is authorized to charge or credit Deposit Account Number: **50-0311**, Customer Number: **35437**, Reference Number: **27353-513 US1**.

Respectfully submitted,

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